Pre-therapy inflammation and long-term CD4 response to antiretroviral therapy

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INTRODUCTION

- CD4+ cell count response to ART is an important determinant of serious outcomes in HIV-positive individuals
- Pre-ART levels of inflammation and coagulation markers are associated with the risk of long-term outcomes[1-3]
- It is unknown whether pre-ART inflammation predicts long-term gain in CD4+ cell count post ART initiation
  - High pre-ART immune-activation could potentially result in attenuated gain in CD4+ cell count
- Exploring this relationship could provide a mechanistic insight in to the process of how inflammation relates to clinical outcomes

STUDY AIM

- To investigate whether pre-ART inflammation and coagulation activation predict CD4+ cell count response to ART in HIV-positive patients (re)initiating ART at a wide range of baseline CD4+ cell counts.

METHODS

- **Study population:**
  - SMART study participants who were ART naive or off ART at randomisation, subsequently (re)initiated ART and had biomarkers measured at randomisation[4,5]
  - FIRST study participants (all of which were ART-naïve at randomisation) who had biomarkers measured as the part of previous case-control studies[2,6]
- **Outcome:** Absolute change in CD4+ cell count during the follow-up from (re)start of ART (visit 0) to 24 months post-ART. The CD4+ cell count change was calculated by subtracting CD4+ cell count at each follow-up visit from that at ART initiation
- **Main covariates:**
  - Biomarkers of immune-activation/ inflammation: **C-reactive protein (CRP) and interleukin-6 (IL-6)**
  - Biomarker of thrombosis **D-dimer**
  - **'Inflammation score'** generated by adding the rank of the each patient according to the level of each of the markers. Thus a higher score reflects high immune activation/ inflammation and coagulation activation.
  - All markers measured at randomisation (pre-ART) and analysed as quartiles
- **Statistical methods:**
  - Follow-up commenced at the (re)initiation of ART.
  - We plotted mean change in CD4+ cell count at each visit by the quartiles of each baseline biomarker.
  - We then fitted random effects linear models to model change in CD4+ cell count. Time was modelled as visits at months 1, 2, 4, 6, 8, 10, 12, 16, 20, and 24.
  - Models were adjusted for the following baseline (at ART initiation) variables: age, CD4+ cell count, sex, race, mode of transmission, hepatitis B and C status, body mass index, history and duration of any prior ART (if any), duration or date of HIV infection (if known), treatment arm, and log(base 10) of viral load copies/mL.

RESULTS

- A total of 1084 participants with 8264 CD4+ cell count determinations were included in this analysis. Of these, 659 patients were from SMART (26% ART naïve) and 425 from FIRST.
- 75% were male with the mean age of 42 years, 47% were Black, 22% reported IDU as mode of transmission, and 9.6% and 32.8%, respectively, were known to be hepatitis B and C positive.
- The medians (inter-quartile ranges (IQR)) of key variables at ART (re)initiation were as follows: CD4+ cell count: 360 (265-473), D-dimer: 0.43 (0.25-0.81) µg/mL, CRP: 1.69 (0.69-4.12) µg/mL and IL-6: 2.59 (1.63-4.45) pg/mL.
- The median (IQR) CD4+ cell count in SMART and FIRST was 416 (350-530) and 100 (22-300) cells/mm^3, respectively.
- **All of the markers showed an inverse correlation with the baseline CD4+ cell count**, largely driven by a strong correlation in the FIRST cohort (P<0.05 for interaction between baseline CD4 count and the study). In FIRST, the coefficient for each marker (95% confidence interval) per 100 cell increment in baseline CD4+ count were: D-dimer: -0.11 (-0.16, -0.06); IL6: -1.11 (-2.03, -0.18); and CRP: -1.30 (-2.24, -0.37).
- **Figure-1 shows the mean CD4+ cell count change by the quartile (Q1 to Q4) of each biomarker at baseline, overall and separately for each trial.**
- **Table-1** provides the adjusted mean difference in CD4+ cell count change across all visits for quartiles of each biomarker from random effect models. Each model was adjusted for visits (time) and covariates mentioned above.
- **There did not appear to be any relationship between baseline biomarker levels and mean change in CD4+ cell count post ART initiation**

Table-1: Adjusted differences in mean CD4+ cell count change post ART initiation by quartiles of each of immune-activation/inflammation and coagulation markers and baseline CD4+ cell count.

Covariate	Difference in mean CD4 count change relative to reference (95% CI), P-value			
Quartiles of the Biomarker	**IL-6**	**CRP**	**D-dimer**	**Inflammation Rank-score**
1	Reference	Reference	Reference	Reference
2	-2.71 (-21.94 to 16.52), 0.78	1.01 (-18.30 to 20.31), 0.92	-20.35 (-39.86 to -0.84), 0.04	0.19 (-19.40 to 19.79), 0.98
3	-5.10 (-25.11 to 14.91), 0.62	3.72 (-16.16 to 23.60), 0.71	-7.47 (-27.39 to 12.46), 0.46	7.35 (-12.79 to 27.49), 0.47
4	-11.93 (-32.44 to 8.58), 0.25	-0.96 (-21.03 to 19.11), 0.93	-16.32 (-37.15 to 4.51), 0.13	-10.94 (-31.82 to 9.94), 0.31
P for trend	**0.25**	**0.97**	**0.29**	**0.44**
Baseline CD4 count cells/mm^3				
<50	Reference	Reference	Reference	Reference
50-200	6.70 (-19.41 to 32.80), 0.62	6.74 (-19.40 to 32.88), 0.61	5.75 (-20.35 to 31.85), 0.67	5.77 (-20.39 to 31.92), 0.67
200-350	9.72 (-18.58 to 38.02), 0.50	11.15 (-17.06 to 39.37), 0.44	9.26 (-19.05 to 37.58), 0.52	10.17 (-18.08 to 38.42), 0.48
350-500	-12.45 (-41.77 to 16.87), 0.41	-10.74 (-39.95 to18.48), 0.47	-11.46 (-40.76 to 17.84), 0.44	-11.41 (-40.66 to 17.85), 0.44
>500	-39.60 (-71.32 to -7.87), 0.01	-38.75 (-70.51 to -7.00), 0.02	-39.34 (-71.08 to -7.59), 0.01	-39.59 (-71.28 to -7.90), 0.01

Fig 1a: CD4 count change by IL6

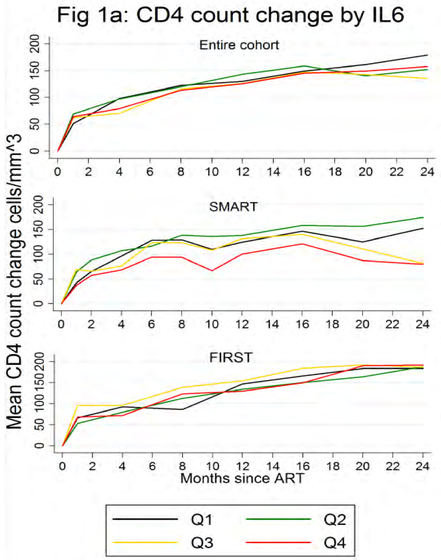


Fig 1b: CD4 count change by CRP

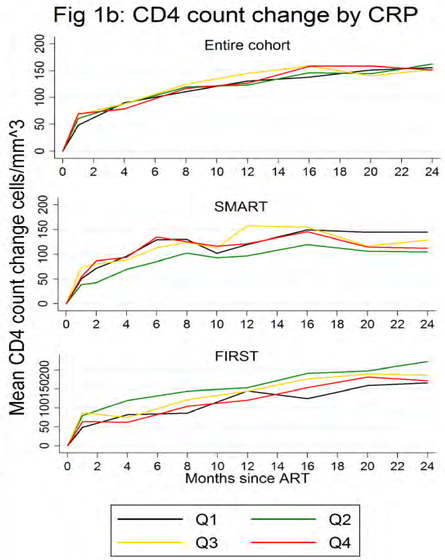


Fig 1c : CD4 count change by D-dimer

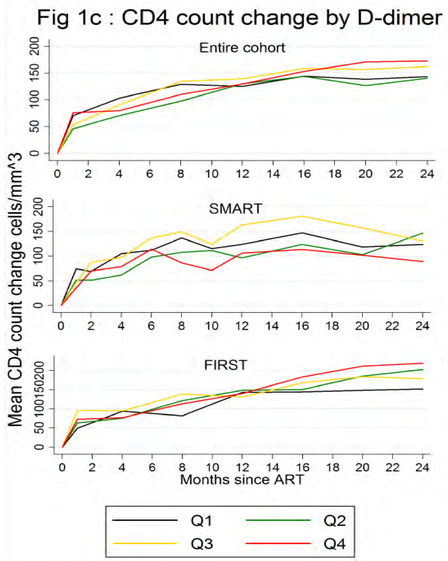
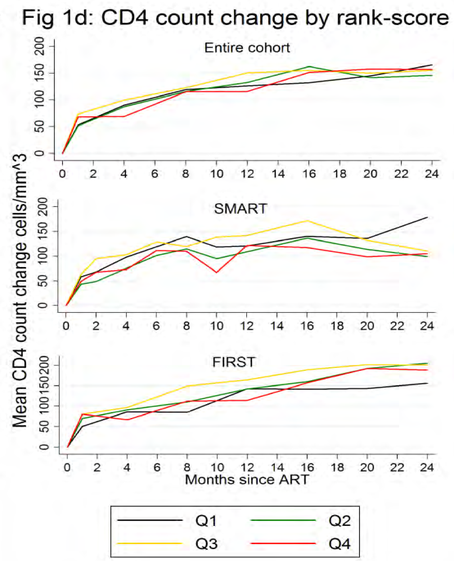


Fig 1d: CD4 count change by rank-score



CONCLUSIONS

- Pre-ART immune-activation/inflammation and coagulation activation levels do not predict CD4+ cell count response to ART.
- They likely influence the risk of clinical outcomes through mechanisms independent of blunting the long-term CD4+ cell count gain.
- Findings indirectly imply that the potential benefit of suppressing pre-ART immune-activation/inflammation (e.g. by anti-inflammatory agents) may not be apparent in the CD4+ cell count trajectory over time

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Acknowledgements: This work was supported by the National Institute of Allergy and Infectious Diseases, National Institutes of Health [grant numbers: U01AI042170 and U01AI46362 (SMART); U01AI042170, U01AI046362, and U01AI068641 for the FIRST Study (CPCRA 058) and INSIGHT, as well as through the Intramural Research Program of NIAID. In addition, this project has been supported in part by federal funds from the National Cancer Institute, National Institutes of Health, under Contract No. HHSN261200800001E. D. R. B. is supported by NIAID grant K23AI073192-02, and J. V. B. by grant K12RR023247-05. We would like to acknowledge the SMART and FIRST participants, the SMART study team (See N Engl J Med 2006;355:2283-96 for the list of investigators in SMART), the FIRST study team (See J Infect Dis. 2011;203:1637 – 46 and Lancet. 2006;368(9553):2125-35 for list of investigators), the INSIGHT Executive Committee.